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Research Article

Molecular Docking Study of Substituted Benzamide Derivatives as Analgesic Candidates

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Abstract

Thiourea derivatives represent a diverse class of compounds exhibiting a range of pharmacological activities, including antitubercular, analgesic, antiviral, and anticancer effects. Of particular interest is *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide, which is hypothesized to possess analgesic properties. A comprehensive *in silico* molecular docking study was undertaken to evaluate this potential. *In silico* assays, leveraging computer simulations, are invaluable tools for predicting outcomes, generating hypotheses, and accelerating drug discovery. Molecular docking, a prominent *in silico* application, facilitates structure-based screening by computationally assessing the binding affinity of compounds to target proteins. This research specifically aimed to predict the analgesic activity of *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide derivatives. To achieve this, various substituents, including methyl, methoxy, tert-butyl, dimethylamino, and halogens, were strategically incorporated at the ortho, meta, and para positions of the benzoylcarbamothioyl ring, generating a library of novel analgesic drug candidates. Compound activity was primarily evaluated using the rerank score. Additionally, ProTox-3.0 and pkCSM were utilized to predict these synthesized compounds' toxicity and physicochemical properties. Initial findings were encouraging, with 18 derivatives of *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide demonstrating enhanced predicted analgesic activity. Among these, six compounds exhibited promising analgesic properties without predicted toxicity. In conclusion, these *in silico* results suggest that certain *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide derivatives hold significant promise as potential analgesic agents, warranting further validation through subsequent laboratory and *in vivo* investigations.

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INTRODUCTION

Pain and inflammation are complex biological processes often mediated by the cyclooxygenase (COX) enzyme. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used therapeutic agents that exert their analgesic and anti-inflammatory effects by inhibiting COX, thereby reducing the production of prostaglandins[1,2]. There are two main isoforms of this enzyme: COX-1 and COX-2. While COX-1 is constitutively expressed and plays a crucial role in maintaining physiological functions, COX-2 is primarily associated with inflammatory responses, atherosclerosis, and tissue repair[3-6]. Compounds containing thiourea and urea functional groups have shown promise in medicinal chemistry due to their diverse biological activities, including antiviral, antibacterial, analgesic, and anti-inflammatory effects[7]. Previous research has explored the analgesic potential of various thiourea derivatives[8]. For instance, Hardjono *et al.*[9] hypothesized that N-

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benzoylthiourea possesses analgesic properties, while Razak *et al*.[10] found that the urea derivative 1-allyl-3-benzoylthiourea exhibited more potent analgesic effects. Furthermore, Fawwaz *et al*. demonstrated that *N*-allyl-*N*'-benzoylthiourea interacts with the active site of the COX-2 receptor[11]. Interestingly, replacing the oxygen atom in benzoylurea with a sulfur atom to create benzoylthiourea enhances its central nervous system (CNS) depressive effects, likely due to a structural resemblance to barbiturate acid group compounds[12].

Molecular docking is a powerful computational tool that provides valuable insights into drug-receptor interactions. It is frequently employed to predict the binding orientation of small-molecule drug candidates to their protein targets and to estimate their binding affinity and activity[13,14]. By using molecular docking, researchers can systematically modify existing compounds to discover novel active molecules without the need for extensive trial-and-error synthesis[15,16]. This rational approach allows for the efficient identification of promising candidates, which can then proceed to the synthesis and *in vitro* testing phases[17,18].

In this study, we employed molecular docking to identify novel analgesic candidates. We selected *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide, a known analgesic agent among urea derivatives, as our parent compound. We systematically modified this compound by introducing alkyl and halogen groups (such as CH_3, OCH_3, $C(CH_3)_3$, $N(CH_3)_2$, Cl, Br, and I) at the ortho, meta, and para positions. The goal was to analyze the impact of these structural modifications on the compound's analgesic activity. Using diclofenac sodium as a reference standard, our computational analysis successfully identified six modified derivatives with significantly improved activity compared to the parent compound.

MATERIALS AND METHODS

Materials

The computational analysis in this study was performed using a high-performance laptop. The hardware specifications were as follows: Intel Core™ i7-8750H CPU (2.20 GHz), NVIDIA GeForce GTX graphics card, 8 GB of RAM, and a 1 TB HDD. The primary focus of this research was COX-2 receptor. For this purpose, the molecular structure of the receptor was retrieved from the Protein Data Bank (PDB) (www.rcsb.org) with the PDB ID 1PXX, and a resolution of 2.9 Å (**Figure 1**). The file was downloaded in PDB format. The co-crystal ligand used for analysis was diclofenac, also known as 2-((2,6-dichlorophenyl)amino)benzeneacetic acid. Diclofenac is a well-known NSAID that inhibits both COX-1 and COX-2 enzymes, with a more potent and specific inhibitory action against COX-2 compared to other NSAIDs[19]. Prior to molecular docking, a meticulous analysis of the cyclooxygenase active pocket was conducted to identify the key amino acid residues and the precise location of the active receptor site, followed by a rigorous receptor optimization process[20].

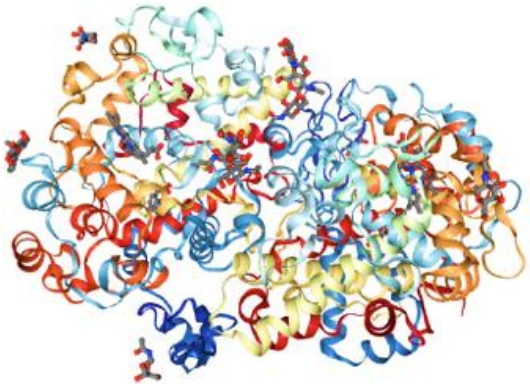


Figure 1. COX-2 receptor with diclofenac as a co-crystal ligand (PDB ID: 1PXX).

Methods

Molecular docking

Molecular docking was performed using Molegro Virtual Docker 5.0. The target protein was validated by separating its crystallographic ligand and re-docking it to confirm the accuracy of the software and the integrity of the protein structure. The validation was successful, with the Root Mean Square Deviation (RMSD) between the redocked and crystallographic

ligands being less than 2 Å, which is a critical criterion for accurate pose prediction and alignment with experimental data[21,22]. The study focused on *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide derivatives, where substitutions of CH_3, OCH_3, $C(CH_3)_3$, $N(CH_3)_2$, and halogens (Cl, Br, I) were made at the ortho, meta, and para positions. Docking was conducted using Molegro Virtual Docker with standard settings, and a cavity detection algorithm was used to identify potential drug binding sites on the protein.

ADMET prediction

Essential physicochemical properties and ADME (Absorption, Distribution, Metabolism, and Excretion) properties were predicted using the pkCSM online platform. The properties assessed included molecular weight (MW), the logarithm of the octanol/water partition coefficient (Log P), number of rotatable bonds, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), and polar surface area (PSA). The compounds were converted into SMILES format using an online translator before being processed by the pkCSM platform. The ProTox-3.0 was specifically used to predict the oral toxicity (LD_{50}) in rodents and to classify the compounds' toxicity according to the Globally Harmonized System (GHS), providing a comprehensive assessment of their safety profiles.

Data analysis

To analyze the molecular docking data, the binding energies of the synthesized *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide derivatives were calculated using Molegro Virtual Docker 5.0, with the lowest binding energy poses or rerank score (RS) selected to identify the most stable conformations. The results were then correlated with ADMET predictions from pkCSM and ProTox-3.0, which assessed key physicochemical properties and toxicity profiles, including LD_{50}, to evaluate the compounds' potential as drug candidates. Finally, the data from both molecular docking and ADMET analyses were integrated to identify the most promising derivatives based on their binding affinity, stability, and safety profile.

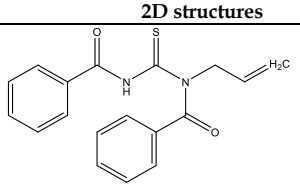
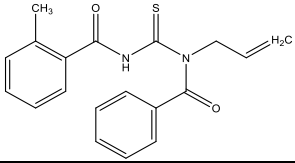
RESULTS AND DISCUSSION

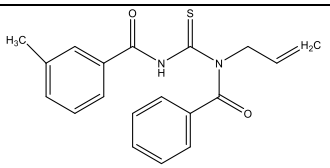
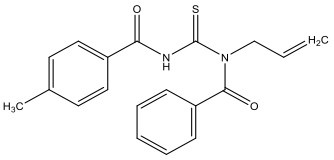
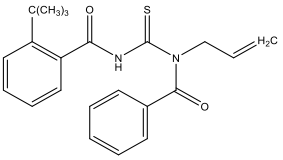
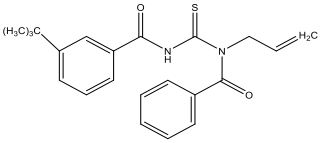
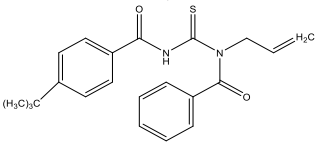
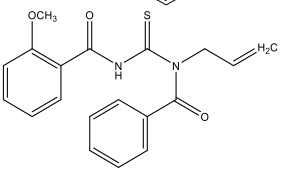
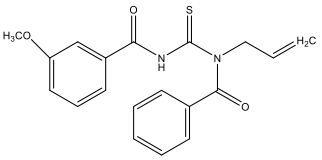
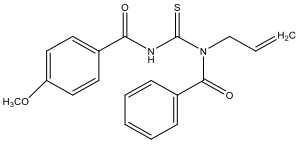
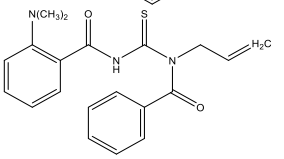
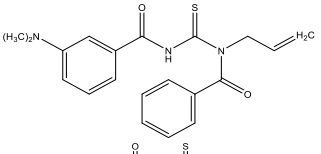
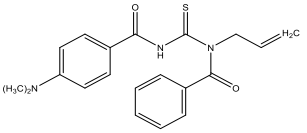
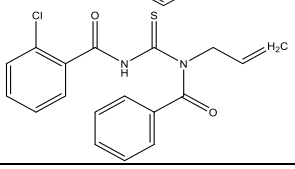
Prior to the main simulations, the docking protocol was validated by separating the native crystallographic ligand from the target protein and then re-docking it. The results of this validation confirmed the compatibility of the software with the hardware used in this study. The success of the validation was evidenced by the near-identical conformational shapes of the docked and crystallographic ligands, which were reflected in a very low RMSD value of 0.6 Å. This low RMSD value confirms the accuracy and reliability of the docking method in predicting the correct binding pose of the ligand. The detailed validation results are presented in **Table I**. Prior to docking, the three-dimensional structures of all ligands were prepared using ChemSketch, while the receptor was retrieved from the PDB archive. The two-dimensional structures of all ligands used in this study are presented in **Table II**.

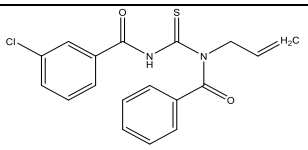
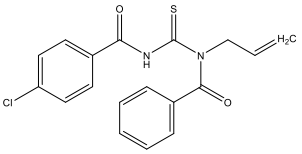
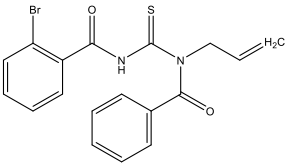
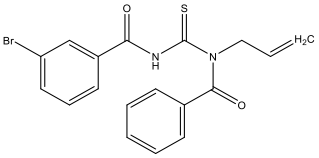
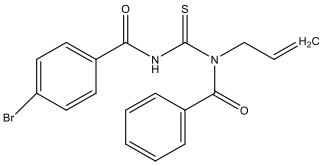
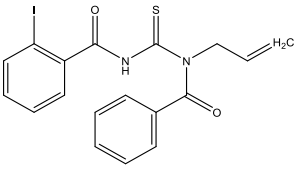
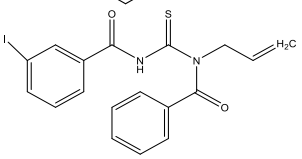
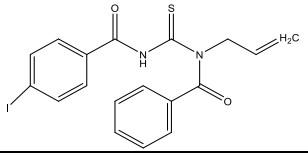
Table I. Validation of 1PXX receptor.

Parameters	Details
Receptor	1PXX
Ligand	2-2[(2,6-dichlorophenyl)amino]benzeneacetic acid
RMSD (Å)	0.6

Table II. 2D structure of test ligand.

Codes	Compounds	2D structures
SI	*N*-allyl-*N*′-(benzoylcarbamothioyl)benzamide	
SI-o-CH_3	*N*-allyl-*N*′-2-methyl(benzoylcarbamothioyl)benzamide	

SI-m-CH_3	*N*-allyl-*N*′-3-methyl(benzoylcarbamothioyl)benzamide	
SI-p-CH_3	*N*-allyl-*N*′-4-methyl(benzoylcarbamothioyl)benzamide	
SI-o-$C(CH_3)_3$	*N*-allyl-*N*′-2-tert-butyl(benzoylcarbamothioyl)benzamide	
SI-m-$C(CH_3)_3$	*N*-allyl-*N*′-3-tert-butyl(benzoylcarbamothioyl)benzamide	
SI-p-$C(CH_3)_3$	*N*-allyl-*N*′-4-tert-butyl(benzoylcarbamothioyl)benzamide	
SI-o-OCH_3	*N*-allyl-*N*′-2-methoxy(benzoylcarbamothioyl)benzamide	
SI-m-OCH_3	*N*-allyl-*N*′-3-methoxy(benzoylcarbamothioyl)benzamide	
SI-p-OCH_3	*N*-allyl-*N*′-4-methoxy(benzoylcarbamothioyl)benzamide	
SI-o-$N(CH_3)_2$	*N*-allyl-*N*′-2-dimethylamine(benzoylcarbamothioyl)benzamide	
SI-m-$N(CH_3)_2$	*N*-allyl-*N*′-3-dimethylamine(benzoylcarbamothioyl)benzamide	
SI-p-$N(CH_3)_2$	*N*-allyl-*N*′-4-dimethylamine(benzoylcarbamothioyl)benzamide	
SI-o-Cl	*N*-allyl-*N*′-2-chloro(benzoylcarbamothioyl)benzamide	

SI-m-Cl	*N*-allyl-*N*′-3-chloro(benzoylcarbamothioyl)benzamide	
SI-p-Cl	*N*-allyl-*N*′-4-chloro(benzoylcarbamothioyl)benzamide	
SI-o-Br	*N*-allyl-*N*′-2-bromo(benzoylcarbamothioyl)benzamide	
SI-m-Br	*N*-allyl-*N*′-3-bromo(benzoilkarbamotioil)benzamide	
SI-p-Br	*N*-allyl-*N*′-4-bromo(benzoylcarbamothioyl)benzamide	
SI-o-I	*N*-allyl-*N*′-2-iodo(benzoylcarbamothioyl)benzamide	
SI-m-I	*N*-allyl-*N*′-3-iodo(benzoylcarbamothioyl)benzamide	
SI-p-I	*N*-allyl-*N*′-4-iodo(benzoylcarbamothioyl)benzamide	

Molecular docking is a powerful computational technique used to model the atomic-level interactions between small molecules and proteins, which helps to characterize their behavior at binding sites and provides insights into underlying biochemical processes[23]. This study utilized Molegro Virtual Docker for protein-ligand docking simulations to computationally determine the optimal position of potential drug candidates at their protein targets. This method is crucial in computer-aided drug design as it provides a cost-effective and efficient way to evaluate a ligand's binding affinity for a target protein, thereby identifying the most promising candidates for further investigation[24].

The molecular docking analysis focused on evaluating the physicochemical properties, toxicity, and receptor activity of the tested compounds. The physicochemical analysis, conducted using the pkCSM online tool, adhered to Lipinski's rule of five, a widely accepted framework for predicting a compound's oral bioavailability and drug-likeness. This rule assesses a compound's potential to cross cell membranes by evaluating four key criteria: a molecular weight less than 500 Da, a Log P value less than five, fewer than five hydrogen bond donors, and fewer than ten hydrogen bond acceptors[25]. In parallel, the toxicity of the 21 compounds was predicted using the ProTox-3.0, which categorizes them into different toxicity classes. A comprehensive summary of the compounds' physicochemical properties, toxicity profiles, and predicted activity is provided in **Table III**.

Table III. *In silico* prediction of physicochemical properties, toxicity and activity of *N*-allyl-*N*'-(benzoylcarbamothiol)benzamide derivatives.

Compounds	Lipinski's rule of five	Rerank score (RS)	Toxicity	
			Hepatotoxicity	LD_{50} (mg/kg)
SI	Yes	-85.2661	No	955
SI-o-CH_3	Yes	-83.4051	No	1950
SI-m-CH_3	Yes	-91.6221	No	1170
SI-p-CH_3	Yes	-98.3012	No	1460
SI-o-$C(CH_3)_3$	Yes	-86.6366	No	330
SI-m-$C(CH_3)_3$	Yes	-99.5266	No	1170
SI-p-$C(CH_3)_3$	Yes	-104.01	No	2000
SI-o-OCH_3	Yes	-92.3491	No	3000
SI-m-OCH_3	Yes	-90.3764	Yes	2080
SI-p-OCH_3	Yes	-102.027	Yes	3000
SI-o-$N(CH_3)_2$	Yes	-95.0171	No	2850
SI-m-$N(CH_3)_2$	Yes	-98.999	No	1600
SI-p-$N(CH_3)_2$	Yes	-85.3768	No	2850
SI-o-Cl	Yes	-95.1832	No	2000
SI-m-Cl	Yes	-99.3883	No	1450
SI-p-Cl	Yes	-98.1472	No	1250
SI-o-Br	Yes	-93.4672	No	2000
SI-m-Br	Yes	-91.2053	No	2000
SI-p-Br	Yes	-95.2357	No	2000
SI-o-I	Yes	-91.8082	No	955
SI-m-I	Yes	-99.6306	No	1200
SI-p-I	Yes	-94.4424	No	955

All 21 compounds evaluated in this study successfully complied with Lipinski's rule of five, a key metric for predicting oral bioavailability and drug-likeness. The toxicity analysis, based on data from the pkCSM, included predictions for hepatotoxicity, LD_{50} (mg/kg), and a GHS toxicity class. The GHS classification system ranks toxicity from Class 1 (most toxic, LD_{50} <5 mg/kg) to Class 5 (least toxic, unspecified LD_{50}), where a higher-class number indicates lower toxicity[26].

The RS values, which indicate binding affinity, ranged from -83.4051 to -104.01 for the *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide derivatives. Notably, all derivatives exhibited a higher predicted affinity for the target protein compared to the reference drug, diclofenac, which had an RS value of -95.16. This suggests that all compounds possess potential inhibitory activity. For instance, the addition of an ortho-methyl group decreased activity (RS = -83.4051), while adding an OCH_3 group at the meta and para positions significantly increased activity (RS = -90.3764 and -102.027, respectively). However, these latter compounds were also predicted to be hepatotoxic, making them unsuitable for further development despite their high affinity.

Based on these results, six compounds were selected for potential synthesis and further research due to their combination of high predicted analgesic activity and a lack of hepatotoxicity. These selected compounds—including *N*-allyl-*N*'-4-methyl(benzoylcarbamothioyl)benzamide and *N*-allyl-*N*'-4-tert-butyl(benzoylcarbamothioyl)benzamide—exhibited RS values ranging from -98.3012 to -104.01 kcal/mol, among the lowest scores in the dataset. A lower RS value indicates a more stable and energetically favorable interaction between the ligand and the receptor, signifying a stronger binding affinity. The selection of exactly six compounds is justified by previous research, which suggests that a minimum of four to six compounds is necessary to establish a reliable quantitative structure-activity relationship (QSAR) equation, thereby providing a foundational basis for future activity assays and the development of a comprehensive model for the entire derivative series[27].

The molecular docking analysis also shed light on the crucial amino acid residues involved in the inhibition of the target protein, COX-2. Our findings confirm that Ser-530 and Tyr-385 are critical active site residues, aligning with previous studies[6,19]. The strong binding affinity of the ligands appears to be mediated by key interactions with these residues. As shown in **Table IV**, all six selected compounds form specific interactions with the 1PXX receptor, and their 2D and 3D interactions can be visualized in **Figure 2**. The 2D visualization with dotted lines illustrates the hydrogen bonds that are critical for molecular structure, properties, and function. The key amino acid residues involved in these interactions include Tyr-355, Tyr-385, Ser-530, Arg-120, and Trp-387. Specifically, the six selected compounds consistently formed hydrogen bonds with Tyr-385 and Ser-530 within the binding cavity, suggesting a potential mechanism of action through the inhibition of prostaglandin synthesis.

Table IV. 1PXX receptor target amino acids that interact with six selected compounds.

Compounds	Hydrogen bonds	Steric bonds
SI-p-CH_3	Tyr385, Ser530	Arg120, Leu352, Trp387, Phe198, Phe518, Val523
SI-m-$C(CH_3)_3$	Ser530	Leu531, Val349, Leu352, Tyr385, Ala527, Phe529, Ser530, Gly526, Val523, Phe381
SI-p-$C(CH_3)_3$	Tyr385	Ala527, Leu531, Leu352, Tyr385, Tyr348, Gly526, Ser530, Phe381, Leu534
SI-m-$N(CH_3)_2$	Tyr355, Ser530, Tyr385	Phe518, Tyr348, Phe198, Val523, Leu352, Trp387, Tyr355
SI-m-Cl	Tyr385, Ser530	Tyr355, Trp387, Leu352, Val523, Phe518, Phe198
SI-o-I	-	Tyr348, Arg120, Tyr355, Ser530, Gln192, Ser353, Gln350, Val349, Tyr348, Leu352

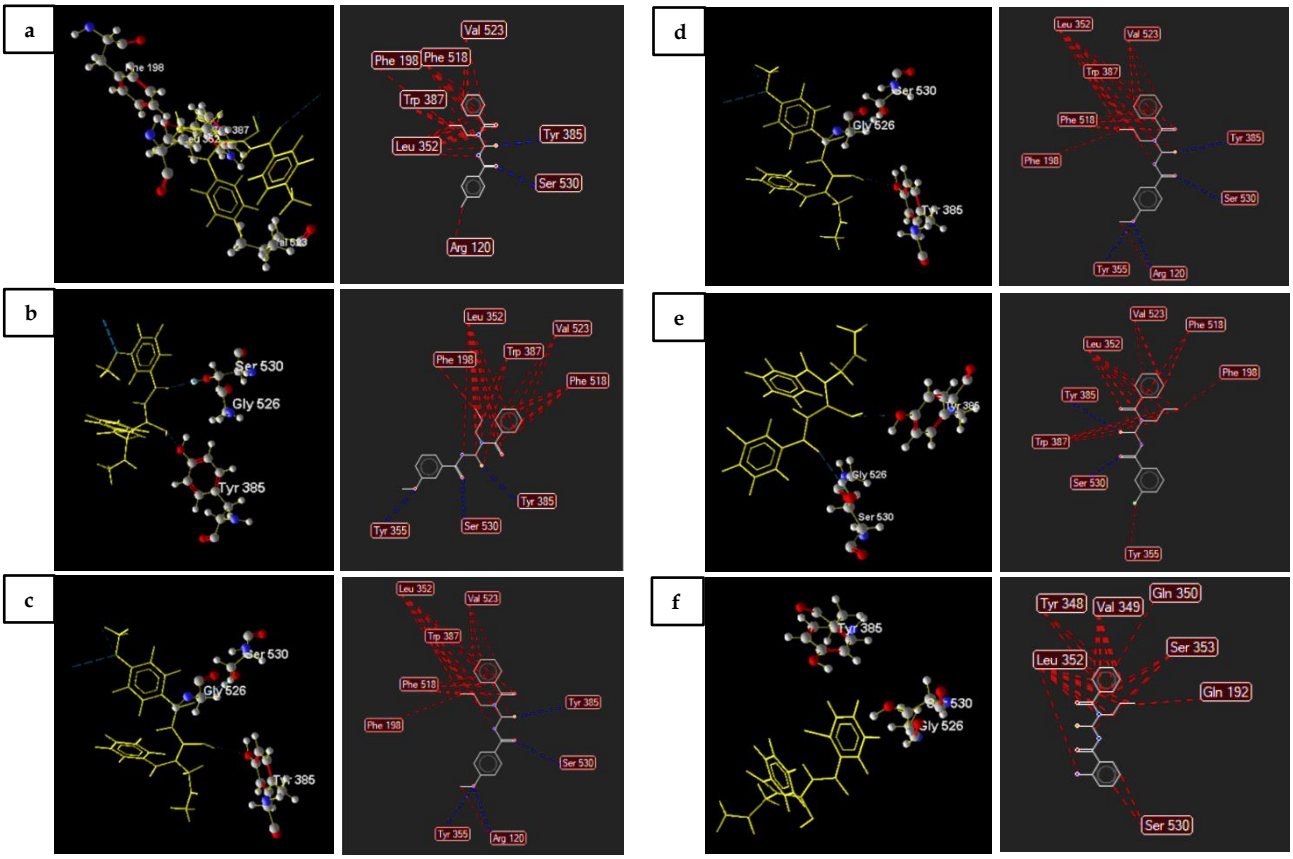


Figure 2. 3D (left) and 2D (right) visualization of six selected compounds: **a)** SI-p-CH_3, **b)** SI-m-$C(CH_3)_3$, **c)** SI-p-$C(CH_3)_3$, **d)** SI-m-$N(CH_3)_2$, **e)** SI-m-Cl, **f)** SI-o-I.

While valuable for predicting molecular interactions and potential mechanisms, molecular docking studies have inherent limitations that must be acknowledged. These simulations are based on static protein structures, often sourced from crystallographic data, which fail to capture the dynamic and flexible nature of biomolecules in a living system. Furthermore, docking algorithms simplify the complex cellular environment by neglecting factors such as solvent effects, protein dynamics, and the broader cellular context, all of which can significantly influence binding interactions[29]. The scoring functions used to estimate binding affinities may also be inaccurate, potentially leading to false-positive or false-negative results. Consequently, without subsequent experimental validation—such as *in vitro* binding assays or *in vivo* pharmacological studies—the predictions from molecular docking remain theoretical. Therefore, to ensure reliable and biologically relevant conclusions, these computational findings should always be integrated with and supported by experimental evidence.

CONCLUSION

The strategic modification of the parent compound *N*-allyl-*N*'-(benzoylcarbamothioyl)benzamide successfully yielded 21 derivatives, of which six demonstrated optimal analgesic activity with the lowest RS values and a favorable non-hepatotoxic profile. These promising compounds warrant further investigation through *in vitro* and *in vivo* experiments to validate their efficacy and safety as potential analgesic agents.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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